REMARKS/ARGUMENTS

Claims 16, 19 to 26, 29 and 30 have been amended for formal purposes.

Claims 16 and 19 to 26 have been amended to correct spelling errors and format inconsistencies.

Claims 29 and 30 were objected to because of informalities. Applicants have adopted the Examiner's suggestion and accordingly amended claims 29 and 30.

Claims 16 to 25 and 27 to 30 have been rejected under 35 U.S.C. §103(a) as unpatentable over CA 2,068,366 to Morella et al. ("CA '366") in view of U.S. Patent No. 5,635,200 to Douglas et al. ("Douglas"). It is submitted this rejection is improper and should be withdrawn.

The present invention is a pharmaceutical formulation. Prior to the present invention, the preferred method of production of microcapsules was by spray drying from a solution. However that method would not produce a coating powder having sustained release properties. While not wishing to be bound by theory, the traditional teaching was that sustained release properties could not be obtained by spray drying because the resulting coating was too porous. The speculation was that the porous coating resulted because of the formation of blow holes in the final coating. While not necessarily deleterious to the taste masking properties of the coating, such a porous coating compromised the sustained release properties. Therefore, the conventional wisdom was that a spray drying process would not produce a particle having both adequate taste masking and sustained release properties. See the previously submitted Deasy article.

In contrast to that teaching, Applicants have overcome these problems as evidenced by the bioavailability study shown in Table 2 of the present specification which demonstrates that the powders of the present invention provide sustained release properties when compared to non-coated products. Accordingly, the present invention provides a significant improvement over the prior art.

Applicants discovered that the presence of "fine" drug particles leads to an increased rate of drug release after coating with a polymer. This was thought to be due to the increased drug surface area that in turn led to a thinner polymer coating when common amounts of polymer were utilized. Initially, the Applicants thought (as did others in the art) that control of drug particle size was the only important factor. Applicants subsequently discovered that particle shape was potentially an important parameter. Two test batches, D4426 and D4427, were treated to determine the effect of needle shaped particles. Attached to the enclosed (and previously submitted) Lukas Declaration are electron micrographs of powder of test batches D4426 and D4427. Batch D4426 was utilized as supplied by the supplier. As can be readily seen from the electron micrograph in Batch D4426 (which details the material provided by the supplier), a certain number of particles are effectively oblong in shape and contain sharp edges and are outside the now claimed aspect ratio. In contrast, the electron micrograph of Batch D4427 does not demonstrate particles with these dimensions. Further, a more homogenous particle size distribution also improves the performance characteristics. When these batches of particles were subjected to the process described, it was found that the needle shaped particles produced a material where 19% of the material was released after 40 minutes which is unacceptably high. In contrast, the more homogeneous batch D4427 only demonstrated 8% release after 40 minutes. This was therefore an acceptable release profile. The results of these trials are discussed in the enclosed Lukas Declaration.

The spray drying process as described in the present application as understood by one skilled in the art involves the dispersion of the active constituents and the polymeric coating in a solvent followed by evaporation of the solvent through the use of a spray dryer. Generally, the solubility of the drug to be used in the solvent is lower than the solubility of the coating agent in the solvent. Accordingly, as the solvent particles evaporate, the active agents crystallize and a liquid coating, which comprises the solvent and the still dissolved coating polymer, form about them.

With continued solvent evaporation, the coating polymer is no longer soluble in the remaining solvent and crystallizes forming a continuous polymer coating around the active drug (which acts as a seed crystal for the polymer). This leads to the improved coating properties of the present invention as it affords almost a discrete core of active constituent surrounded by a discrete polymer coating. Furthermore, in some cases of spray drying the solvent is chosen so as not to dissolve the active ingredient at all i.e. the active ingredient stays crystalline throughout the process, and during the spray drying process the polymeric coating dries around the already crystalline active ingredient.

The Office Action asserts that CA '366 essentially shows every feature of the invention as defined in claims 16 to 25 and 27 to 30 but for the aspect ratio of less than 3 and a spherical shape wherein the spherical particle has an aspect ratio of 1. Applicants respectfully disagree.

The Examiner cites to page 4, lines 15 to 23, and contends that the reference shows that the coating of the dosage form can be from 10 to 80% of the formulation. However, such statements cannot be taken alone out of context from this multipage document. For example, at page 15, line 16 to 26, the reference lists the different parameters which are involved to obtain a microcapsule coating composition with a particular release profile for the material. In view of this extensive list of parameters, it is submitted that while the reference may use broad language to describe the wt. -% of the coating, the Examiner must consider the entire reference. The reference examples show that the coating weight of the dosage forms varies from a low of approximately 30% to a high of 55%. In this regard, the Examiner should note that methylene chloride and dichloromethane (another name for methylene chloride) are the named solvents used in the spray drying operation and those solvents are flashed off during the spray drying procedure and are not part of the dosage forms product. Of particular significance is Example 6 which is a comparative example which incorporates a coating weight of approximately 27 wt.-%. The product of that comparative example is viewed under a scanning electron microscope ("SEM") and the results illustrate that the product

exhibited little taste-masking consistent with the porous structure of that product as is illustrated in reference Figures 7(a) and (b).

None of the reference examples appear to illustrate a dosage form wherein the coating weight is as little as 10% or even less than the limit ("23%") now set forth in the pending claims. Thus, CA '366 does nothing more than extend an invitation to experiment and does not provide sufficient guidance to one of ordinary skill in the art to obtain a dosage form with both taste masking and sustained release properties when produced by a spray drying process with a coating weight of 23 wt.-% or less. CA '366 does no more than confirm Applicant's statement on page 1, lines 28 to page 2, line 3, of the specification that coating weights less than 24% gave unsatisfactory taste masking when that dosage form was produced by spray drying procedures. The reference itself establishes in Example 6 that coating weights as low as 27 wt.-% do not give taste masking properties. CA '366 does not exemplify an embodiment of the invention with such a relatively low coating weight. Thus, the disclosure relied on by the Examiner is not actually an enabling disclosure for the purpose for which it is cited.

Douglas relates to taste masking compositions of ranitidine and specifically to ranitidine hydrochloride. Douglas' comment as to particle size is based on his desire to avoid a "gritty" feel in the mouth.

In Douglas, the active ingredient is first coated with a lipid phase. The lipid coating is selected from fatty acids or monohydric alcohols of those fatty acids, fixed oils, fats, sterols, phospholipds, glycolipids and mixtures thereof. The lipid coated particles of ranitidine are then encased in a binder selected from the group of polyvinyl pyrrolidone, acrylate polymers and cellulose based polymers. The coating weights in Douglas far exceed the upper limits specified in the now pending claims. In fact, it appears that the coating weight percentages of the Douglas examples exceed even the highest coating wt. -% of those exemplified in CA '366. Each of

examples 1 to 3 of Douglas shows the ranitidine hydrochloride content of the final dosage form as 20 wt. -% suggesting that the combined coating and binder weights were approximately 80% in each instance. The particles produced by Example 4 have four times the weight of the tripalmitate relative to the ranitidine hydrochloride. The particles produced in Example 5 also have four times the tristerate and trilaurate relative to the active ingredient. Examples A through G of the reference use artificial sweeteners such as xylitol, peppermint flavoring, aspartame and combinations thereof. It appears that in each of Examples A through G, the active ingredient comprises no more than 20 wt. -% of the dosage form suggesting that the coating and sweetener weights constitute 80 wt.-%.

While the Examiner may be relying on Douglas only for the discussion of the aspect ratio or physical shape of the particles used by Douglas, it is submitted that the command of 35 U.S.C. §103 requires that the entirety of the reference be considered. In this regard, it should be noted that Douglas provides absolutely no information as to the dissolution characteristics of his dosage forms. That is to say, one cannot tell whether those dosage forms are sustained release, controlled release or immediate release products. Douglas' disclosure as to the weight ranges for the lipid and for the binder make it clear that a product according to Douglas could not have a coating weight of 23 wt.-% or less.

Claim 26 has been rejected under 35 U.S.C. §103(a) based on the combination of CA '366 in view of Douglas and further in view of U.S. Patent No. 4,808,411 to Lu et al. ("Lu") or U.S. Patent No. 5,707,646 to Yajima et al. ("Yajima"). It is submitted that this rejection is also improper and should be withdrawn.

Nothing in the Office Action discussion of the Yajima or Lu '411 references or in either of the references indicates that a substantially continuous polymer coating is formed and that the resulting product has sustained release properties or that the coating comprises less than 23% by weight of the formulation.

The Lu '411 reference discloses a complex of carbomer (acrylic acid polymers) and erythromycin or a derivative thereof. Lu's compositions are prepared by dispersing the drug, such as erythromycin, in a suitable organic solvent such as ethanol or acetone, and dispersing the carbomer separately in ethanol, mixing the two solutions slowly to allow formation of the reaction product and then evaporating most of the solvent and diluting the solution with water. The reaction product is recovered by filtration and is then dried. No mention is made of spray drying or spray dried particles. This reference gives no indication of the weight percent of the coating. The Examiner apparently cites Lu for its disclosure of particle size range. However, none of the particle size ranges disclosed in Lu correspond with, or suggest, those set forth in the pending claims. A mention in a reference of particles smaller than 297 microns does not disclose or suggest the parameters set forth in the now pending claims.

Yajima relates to a taste masked pharmaceutical formulation comprising clarithromycin but is no more pertinent than Lu '411 as discussed above.

In summary, Applicants have discovered the parameters in relation to the use of a small amount of polymer coating to successfully achieve taste masking and sustained release properties for pharmaceutically active compounds. These parameters include control of the shape of the core particle which leads to a product with successful performance characteristics.

As shown above, based on the prior art, the release and/or taste masking properties obtained were inconsistent which is not acceptable for pharmaceutical administration. In contrast, formulations in accordance with the present invention exhibit consistency of taste masking and sustained release, leading to improved results. See the enclosed Lukas Declaration. Accordingly, it is respectfully submitted that the invention is not obvious in view of the art.

It is further submitted that the combinations of references are improper. As discussed above, each of the references list different techniques to obtain different products with different

characteristics. It is clear that the Examiner has engaged in a pick and choose technique based on hindsight using Applicants' invention as a blueprint to selectively edit the cited references. This is improper. See *In re Grabiak*, 226 U.S.P.Q. 870 (Fed. Cir. 1985). Further, the manner in which the Examiner has edited the references for the combination would require that salient features of the respective disclosures of the references and important features of the inventions as disclosed therein be ignored. Note the different coating weight in CA '366 and Douglas as well as the different coating techniques. This is also improper for a rejection under 35 U.S.C. §103. See *In re Ratti*, 123 U.S.P.Q. 349 (CCPA 1959).

In view of the foregoing, reconsideration and allowance of the application with claims 16 to 30 are earnestly solicited.

It is believed that no additional fees or charges are required at this time in connection with the present application; however, if any fees or charges are required at this time, they may be charged to our Patent and Trademark Office Deposit Account No. 03-2412.

Respectfully submitted,
COHEN, PONTANI, LIEBERMAN & PAVANE

By _____

Vincent M. Fazzari, Reg. No. 26,879
551 Fifth Avenue, Suite 1210
New York, New York 10176
(212) 687-2770

Dated: April 23, 2004

Encl. Lukas Declaration w/attachments